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THE SPECIFICITY, DANGER, AND ACCURACY OF THE TUBERCULIN TESTS.[1]

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During the past ten years a great change of opinion has taken place in regard to the tuberculin test. The subcutaneous test with its disagreeable reaction has deterred many from using tuberculin diagnostically, and not until von Pirquet described his cutaneous modification and Wolff-Eisner and Calmette their conjunctival test, has tuberculin been universally used. These and other modifications have greatly extended our knowledge of this subject and it has seemed fitting at this time to review briefly my experience with tuberculin used for diagnosis and to draw whatever conclusion about its value that seem warranted.

1. The Specificity of Tuberculin. However it may be with diseases not transmissible to the ordinary laboratory animals, certainly among these animals only those react to the tuberculin tests which are tuberculous. Tuberculin, as Citron and others have shown, is not an ordinary toxin. Normal animals have tuberculin tolerance but no tuberculin anaphylaxis; tuberculous animals have tuberculin anaphylaxis and acquire tuberculin tolerance when properly treated with tuberculin. Normal animals may acquire anaphylaxis after injection of tuberculin when the second dose is

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given intravenously or intracerebrally, but Baldwin and Krause have been unable to produce any sensitiveness to tuberculin in normal guinea-pigs when the second dose is given cutaneously, intracutaneously, subcutaneously, or in the conjunctiva. This suggests that some difference exists between the mechanism involved in the ordinary tuberculin test and that concerned in anaphylaxis, though the difference is probably one only of degree. In Koch's first paper he called attention to the fact that it required 250 mg. to make him react, and in 1891 and again last year, reports have been published showing that infants, apparently healthy, fail to react to very large doses, even 1000 mg. repeatedly given. This simply bears out the experimental fact that only animals infected with tubercle bacilli react.

Many autopsy reports throw grave doubt upon, and personally, I believe, disprove all published statistics which go to show that other diseases (particularly syphilis) react specificially to tuberculin, but indicate that they are in reality instances of double infection. The cutaneous test has shown that patients with these diseases react to tuberculin in about the same proportion as ordinary individuals in poor health. That a slight tuberculous infection may be sufficient to cause reaction for a time and yet leave no permanent pathological change visible to the naked eye, is readily possible.

Leprosy, however, must be considered separately, for the interesting work of Babes suggests that while most of the lepers who react to tuberculin are tuberculous as well, still it is impossible in some to find any evidence of it clinically or at autopsy, and the reddening of the leprous nodules three days after the injection of tuberculin is of considerable interest. The reaction, he believes, is specific for leprosy in that it begins later (twenty-four hours) and lasts longer (for several days) than in the tuberculous, possibly not reaching its maximum until the third or fourth day. The cutaneous test is often absent, while in 50 per cent. of Babes' cases the conjunctival test was positive. Leprosy and tuberculosis are rarely confused, and the presence of lepra bacilli in numbers in the nasal discharge is of great aid in differentiation.

Recent work has tended to show that sensitiveness to the tuberculin tests cannot be produced in healthy individuals. This does away with any fear of a too slow increment of dosage and permits one to use and to draw diagnostic conclusions from a clinical course of tuberculin treatment. A slight reaction to a small dose at any time during the course of treatment would be proof sufficient that the patient had had a tuberculous infection.

2. THE DANGER OF TUBERCULIN.—The conjunctival test has produced a number of unfortunate accidents, one of which, a central corneal opacity, came under my observation after the administration of the test dose. When the subcutaneous test follows a

positive conjunctival test, the eye may react again, or even during tuberculin treatment there may be for a time slight reddening. These objections, with the exception of the injury to sight, are of small moment and when carefully given, excluding all patients who have ever had the slightest trouble with their eyes and using only 1 and 5 per cent. solutions of the old tuberculin, the test seems comparatively safe. General reactions have followed its use, and on the whole it should be avoided in children.

The cutaneous test has produced lymphangitis, extending from the forearm to the elbow or even the shoulder, with slight swelling of the lymphatic glands in several instances, and in another case rather extensive ecchymosis but no necrosis. Several general reactions have occurred in my patients. Certainly the dangers of the cutaneous test are so slight as to warrant no consideration except in scrofulous children.

The subcutaneous test to be positive demands a general reaction, and anyone who has experienced a severe reaction to tuberculin will agree with me that the ordeal is, to say the least, decidedly unpleasant. In the majority of patients the only symptom remaining at the end of the second or third day is a little weakness, which is speedily replaced in many instances by a feeling of improvement. I have repeatedly been asked on this account by these patients for permission to take tuberculin therapeutically. On the other hand, in a few instances, I have seen a slight temperature persist for months after a subcutaneous test when it had been normal previously. In one case expectoration, which had been absent before, was present for two or three years afterward, but it is no uncommon thing for patients who have never had tuberculin to present similar histories. In several instances, on the other hand, patients to whom we were about to administer tuberculin, but for some reason failed to do so, had attacks of pleurisy, hemiplegia, etc.

The discovery for the first time of tubercle bacilli in the sputum just after a subcutaneous tuberculin test, often only indicates that the sputum had not been examined frequently enough before the test. Without doubt tubercle bacilli are present in the sputum of many patients when, after one or two ordinary examinations, they are stated to be absent. In one instance we gave 0.2 and 1 mg. to a patient with negative sputum without reaction of any sort and then found tubercle bacilli in the sputum, which had again become slightly blood-streaked. In another apparently doubtful case, while we were considering the use of the tuberculin test, we found tubercle bacilli in the sputum.

The occurrence of tubercle bacilli in the sputum following or after this test has long been held as proof of the lytic activity which many assume to occur during this reaction. In the 286 tests under consideration, tubercle bacilli were found in the sputum subsequent to the test in 18, fourteen times in the incipient and four in the moderately advanced cases. In order to connect the test with the occurrence of tubercle bacilli as cause and effect, we must establish some limit of time in which the tubercle bacilli must occur. I have arbitrarily chosen two months, but in most instances all effects of the reaction have passed in two or three days. Of these 18 cases, 5 incipient and 2 moderately advanced occurred within this period, 4 within one and 3 within two months. In one instance included here, the test was negative, in another tubercle bacilli were found before a single subcutaneous dose was given while in a third the test was given while the patient was waiting admittance and before the sputum was subjected to as prolonged search as afterward. If we exclude these 3, the figures would indicate that tubercle bacilli are two or three times as likely to occur after as within the time limit of two months. When it is considered that tubercle bacilli occurred after the test in only 6 per cent. of 286 cases, and that in less than 2 per cent. did there occur bacilli within two months after the test, it seems that little weight can be attached to the tuberculin test as the cause of the occurrence of tubercle bacilli in the sputum. If the occurrence of tubercle bacilli in the sputum after the subcutaneous test was connected with the test it is only reasonable to expect to find some signs of congestion and softening in patients whose sputum later showed the presence of tubercle bacilli. In only 2 of the 18 cases previously mentioned were the respiratory symptoms increased, 1 of which was the instance where there was only an intradermic test. In all, 40 patients showed some increase of the respiratory symptoms, and in only 1 could the reaction be considered in any way connected with the occurrence of tubercle bacilli in the sputum. My experience, therefore, leads me to believe that any apparent connection is due entirely to coincidence.

At the Adirondack Cottage Sanitarium, our routine has been to require all patients who have never had tubercle bacilli in their sputum to undergo the subcutaneous test. More recently I have come to hesitate about giving it. When a patient is doing well it is a curious thing that very little seems required to upset the balance and turn, for a time at least, the scale against him. The greatest danger that I have seen result from the subcutaneous test is such a slight temporary disturbance; but without doubt, more danger, however slight, is connected with this test than with the cutaneous or intradermic tests.

3. The Focal Reaction in the Lungs. An increase of physical signs occurred in the lungs in 39 per cent. of 127 patients who were carefully examined, during the reaction and for the most part two days later, or if we include 17 doubtful cases in 45 per cent.

The occurrence of this so-called focal reaction seems to be little connected with the severity of the reaction as manifested either by the symptoms or by the degree of temperature. Symptoms referable to the respiratory tract seem to occur with about equal frequency in those with and in those without increase of physical signs. These respiratory symptoms, however, were in almost every case connected with marked general symptoms, but apparently occurred independently of the degree of fever and showed very little tendency to occur more frequently in early stages of the disease. In a few cases the increased physical signs, persisted, and it is possible that in these and in a few others they were overlooked at the first examination.

4. THE VALUE OF THE TUBERCULIN TEST. A test, to be of real value, should enable us to differentiate not only tuberculosis from other diseases, but also clinical tuberculosis from non-clinical tuberculosis. The latter I define as an infection with tubercle bacilli, which has not reached a stage in which it can be diagnosticated clinically, while the definition of "clinical tuberculosis" is self-evident. Clinical tuberculosis may be masked, active, quiescent, or arrested, stages which can be separated only by the symptoms and physical signs which the patient presents, or by the lack of them.

The occurrence of a tuberculin reaction in apparently healthy men is an interesting phenomenon which would occur probably in a large percentage of middle-aged individuals. It varies, as Franz has shown, more or less directly with the incidence of tuberculosis in the race. It possesses in health no clinical importance, If, however, these same healthy men later fall ill of non-tuberculous diseases, what is going to prevent their reacting, in part at least, to tuberculin? Nägeli's figures and Franz's statistics both warn us of the danger of depending too much upon this test.

In my experience at the Adirondack Cottage Sanitarium, where for several years all patients without tubercle bacilli in the sputum have been required to undergo the subcutaneous test as a routine measure, I have come to believe that failure to react to 10 mg. of old tuberculin, given subcutaneously, does not exclude clinical tuberculosis. However, in the presence of indefinite symptoms, it indicates that in all probability, treatment is unnecessary. I have allowed these patients to return home at once, and so far no doubtful clinical case, which has failed to react to 10 mg. has relapsed, after one to six years, though we have had only 12 such cases. Nine other cases reacted first to 10 mg. One patient who failed to react to 6 mg. was classified as doubtful for several years, but finally relapsed, had tubercle bacilli in his sputum, and tuberculous cervical glands.

I have no doubt that some patients who react to doses much smaller than 10 mg. may suffer only from tuberculous infection, and that the symptoms they present may be due to causes other than tuberculosis. Over one-half (52 per cent.) of our advanced cases reacted to 1 mg. or less, while considerably less than half of the incipient cases (42 per cent.) reacted to the same dose. In only 4 per cent. of the advanced and 15 per cent. of the incipient cases was it necessary to give over 5 mg. to produce reaction. A negative subcutaneous test in a tuberculous patient may indicate either the absence of receptors at the site of the lesion or the presence of free antibodies in the blood. In a certain number of these cases complement deviating substances (amboceptors) have been found in the blood, and in the patient whose clinical history and physical signs point strongly to a diagnosis of tuberculosis, the occurrence of these substances may explain the negative subcutaneous test.

Healthy infants do not react to 1000 mg. Some patients with clinical tuberculosis react only to 10 or more milligrams. There is, therefore, no known limit at which a healthy man will react and no known limit which divides patients with tuberculous infection from those with clinical tuberculosis. Certainly, failure to react to 10 mg. or less does not surely disprove the presence of clinical tuberculosis. Of 9 patients, who failed to react to 10 mg. given subcutaneously, 4 reacted to the cutaneous test, while 3 failed to do so to old tuberculin in full strength, and 2 showed a positive local reaction (Stickreaktion). One of the 3 patients with a negative cutaneous reaction reacted to the intradermic test. The local reaction was positive in every instance (176) where it was noted in patients who reacted to the subcutaneous test.

The cutaneous test is of value in early life, though when its reliability ceases is difficult to determine. Certainly, after seven or eight years, a positive reaction is of little value, for by this time tuberculous infection and clinical tuberculosis are vastly different things, and without doubt the great majority of both react to the cutaneous test. I cannot yet accept a negative skin reaction as excluding either tuberculous infection or clinical tuberculosis, as I know of tuberculous patients in good condition who have failed to react to old tuberculin in full strength. This absence of reaction of the skin or conjunctiva may indicate only that no sessile receptors are present in these parts, not that the patient is without tuberculous infection. Many attempts have been made by graduating the dose in the cutaneous test, to separate clinical tuberculosis from tuberculous infection. Ellerman and Erlandsen believe that they have accomplished this, and suggest the use of a rather complicated formula based upon the differences of the average diameters of the papules when four scarifications have been made through four simultaneously applied doses of tuberculin, each four times stronger than the preceding, for example, 0.5 per cent., 2 per cent., 8 per cent. and 32 per cent. O. T. Some have not been able to verify the work of Ellerman and Erlandsen, nor has it been proved, providing a sufficient amount be used, that the quantity of the solutions plays a very important part. My experience leads me to believe that the more nearly the technique approaches that used for vaccinia, the more reliable the results. In any individual patient, if he react to one drop of 1 per cent. or of a 5 per cent. solution of old tuberculin given in different eyes, he is more likely to have clinical tuberculosis than if he reacted only to the cutaneous test.

The intradermic test should, theoretically, be far more accurate than either the conjunctival or the cutaneous test, however applied, for all the tuberculin given reaches the interior of the skin. It admits further of accurate dosage which, on account of the possible variation in power of absorption of the skin and the difficulty of keeping all the solution over the abrasion or in the conjunctiva until absorbed, is impossible in either the cutaneous or the conjunctival tests. In some instances certainly it is more sensitive than the skin test, reacting where the latter is absent. While a dose of 0.02 of a milligram has never caused a general reaction, we have no record of any patient failing to react to this dose given intradermically.

In brief, if we except for the time being, leprosy, tuberculin is a specific test for the detection of tuberculous infection. The danger from the use of the tuberculin test is slight, but in some unsuitable cases very real and possibly severe. Reaction, even when severe, has no connection with the appearance of tubercle bacilli in the sputum. Increase of physical signs occurs in about one-third of all the cases and in one-half of those with increase of pulmonary symptoms and is independent of the appearance of tubercle bacilli in the sputum. In practice, exposure to infection, characteristic symptoms, such as hemoptysis, pleurisy with effusion, dry pleurisy on both sides, and localized persistent physical signs at one apex, are diagnostic data of far more importance in clinical tuberculosis than that derived from the tuberculin tests. A positive reaction, when only doubtful symptoms of pulmonary tuberculosis are present, is of uncertain value unless the pulmonary symptoms or signs are definitely increased during the reaction. A negative reaction is of uncertain value, and in the face of positive symptoms carries little weight. In many instances the tuberculin tests add only confusion to the clinical data. The subcutaneous test, depending as it does upon the reaction at the site of the lesion, is still today the most reliable of the tuberculin tests; but neither this nor any of the modifications as yet devised, differentiate clearly clinical tuberculosis that demands vigorous treatment from non-clinical tuberculosis that requires only a God-fearing life.

TUBERCULOUS INFECTIONS CLASSIFIED FOR AID IN DIAGNOSIS AND TREATMENT.

A. Diagnosis.

- I. Non-clinical tuberculosis.
  - No symptoms or physical signs.
  - May or may not react to tuberculin tests.
- II. Clinical tuberculosis.
  - With symptoms or physical signs or both.
  - Usually react to tuberculin tests.
    - (*a*) Masked.
      - Physical signs only, no symptoms.
    - (*b*) Active.
      - Symptoms present.
      - Physical signs usually present.
    - (*c*) Quiescent or arrested.
      - Symptoms present now or formerly.
      - Physical signs present or absent.

B. Treatment.

- *A*. Not necessary.
  - I. Non-clinical tuberculosis.
  - II. Clinical tuberculosis.
    - (*a*) Masked.
- *B*. Necessary now or formerly.
  - II. Clinical tuberculosis.
    - (*b*) Active.
    - (*c*) Quiescent or arrested.

IS PERNICIOUS ANEMIA OF INFECTIOUS ORIGIN?[1]

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Since Addison's description, various types of anemia due to carcinoma, sepsis, parasites, etc., have been differentiated, but there is still left a large group of cases for which the title of cryptogenetic pernicious anemia must be preserved. No matter where seen—in Austria, Switzerland, Germany, Paris, London, Boston, or California—these cases are symptomatically remarkably alike. The difficulties of distinguishing the characteristic blood changes from so-called secondary anemias seem to me much exaggerated. Clinically, the general appearance of the patient, the fever, the cardiovascular, gastro-intestinal, and nervous symptoms, the peculiar remissions, pathologically the pronounced fatty degenerations, the siderosis in liver, spleen, and kidneys, the marrow changes, are as characteristic of the disease as the blood picture. The constancy of these phenomena in practically all cases is in favor of a definite clinical entity, the result of some specific intoxication.

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Nearly all authors now agree that the marrow changes are secondary, represent regenerative efforts, and are not in any way specific. Recent investigations have been concerned chiefly with causes of the pathological hemolysis, which is a main feature of the disease. Experimentally by injection of toluylendiamine, ricin, pyridin, saponin, hemolysis may readily be induced and marrow changes and a blood picture may result that closely resemble those of pernicious anemia. Schaumann, Faust, and Tallquist have shown that the anemia due to bothriocephalus is the result of hemolysis produced by a lipoid substance that may be extracted from the segments. In these cases, also, lipoid bodies are to be found in increased amounts in the gastro-intestinal tract. The hemolytic substance isolated by Tallquist was either the sodium or cholesterin combination with oleic acid; normally but little cholesterin was to be found in blood, and when a certain concentration was reached hemolysis occurred. Tallquist suggested therapeutically calcium salts or glycerin to form insoluble or harmless compounds with oleic acid. On the other hand, von Eisler, following the observation of Kruskal that serum inhibited to a certain degree the hemolytic action of saponin, showed that this was due to cholesterin, and Ransome demonstrated that the specific resistance of the erythrocytes was likewise dependent upon cholesterin. In animals, the resistance to saponin hemolysis runs parallel with the cholesterin content of the serum. Morgenroth and Reicher, working with cobra venom and other toxic lecithins, proposed the use of cholesterin therapeutically to inhibit hemolysis. Fejes has recently written of anemia produced experimentally by bacterial hemolysins. Berger and Tsachiya extracted a lipoid substance from the intestinal mucous membrane of individuals dying from pernicious anemia, and found its hemolytic action ten times more potent than extracts from other cases. Anemia of the pernicious type resulted from its injection in animals, a similar lipoid could be obtained from the gastro-intestinal mucous membrane of dogs after production of moderate inflammatory changes. Schlaepfer, employing the method of Ciaccio for preserving lipoids, found lipoid bodies in the intestinal mucous membrane of two cases of pernicious anemia;